Simpson-Golabi-Behmel Syndrome

Rome, November 2009
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Described independently by Simpson et al. (1975), Golabi & Rosen (1984) and Behmel et al. (1984)

Renamed in 1988 by G. Neri & co. as Simpson-Golabi-Behmel Syndrome

Simpson-Golabi-Behmel is an Overgrowth Syndrome

Overgrowth Syndromes. Classification

• Hyperplasia
• Hypertrophy
• Increased interstitial fluid
• Any combination of them
### OGS Classification

<table>
<thead>
<tr>
<th>A - TRUE:</th>
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<tbody>
<tr>
<td>Bannayan-Riley-Ruvalcaba</td>
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<tr>
<td>Beckwith-Wiedemann</td>
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<td>Sotos</td>
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<tr>
<td>Weaver</td>
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<tr>
<td>Macrocephaly/capillary malformation</td>
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<tr>
<td>Simpson-Golabi-Beahmel</td>
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<tr>
<td>Perlman</td>
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<td>Costello</td>
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<tr>
<td>Non-syndromic OGS with or without MR</td>
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<tr>
<th>B - PARTIAL / LOCALIZED</th>
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<tbody>
<tr>
<td>Hemihypertrophy/hemihiperplasia</td>
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<tr>
<td>Klippel Trenaunay</td>
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<tr>
<td>Proteus</td>
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<td>CLOVE</td>
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<td>CLAPO</td>
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<tr>
<th>C - MISCELLENOUS: CHROMOSOMAL- ENDOCRINOLOGY-OTHERS</th>
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<tbody>
<tr>
<td>Chromosomal (Klinefelter; Pallister Killian; Trisomy 8 mosaic; Fragile X;</td>
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<tr>
<td>Duplication 4p16.3; Deletion 22q13</td>
</tr>
<tr>
<td>Endocrinologic (son of diabetic mother; hypophysis)</td>
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<tr>
<td>Other (Marfan/ Homocystinuría)</td>
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The OGS share some common characteristics:

- Increased risk of mental retardation
- Increased risk of tumours
In some disorders:

- Sotos syndrome: ~70%
- Simpson Golabi Behmel syndrome: ~30-50%
- Macrocephaly- Capillary Malf.: ~40%
- Beckwith Wiedemann syndrome: ~2-3%
OGS. Tumoral Risk

High Tumor Risk

- Malignancies
  Perlman
  Simpson-Golabi-Behmel
  Beckwith-Wiedemann
  Hemihypertrophy

- Benign tumors
  Proteus
  Bannayan-Riley-Ruvalcaba
  Klippel-Trenaunay

Mild Tumor Risk

- Malignancies
  Bannayan-Riley-Ruvalcaba
  Klippel-Trenaunay
  Sotos
  Weaver
  Proteus
  Macrocephaly- Capillary Malformation

- Benign Tumors
  Hemihypertrophy
  Beckwith- Wiedemann
SIMPSON-GOLABI BEHMEL SYNDROME

- Overgrowth (mainly in height and weight)
- Coarse face
- Dental crowding
- Cleft palate- Cleft lip
- Polydactyly
- Lipomas and mesenchymatic tumors
- Speech and language problems
- Variable mental retardation
- Increased tumor risk
Established in November 2003 at Hospital Universitario La Paz (Madrid)

About 1200 entries of at least 15 different disorders

Nation-wide with participation of all regions
SGBS- Clinical Findings - Face

- Coarse face
- Hypertelorism
- Large mouth
- Midline groove of tongue
- Cleft lip
- Cleft palate
- Malposition of teeth
- Congenitally missing teeth
- Supernumerary teeth
- Odontogenic keratocysts

SGBS- Facial features
SGBS- Facial features
SGBS-Abdominal problems

- Diaphragmatic herniae
- Hepatomegaly
- Splenomegaly (rare)
- Extra nipples

SGBS- Abdominal findings

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SGBS- Clinical findings
Cardiovascular problems in 26%

- Ischemic stroke (dissection of internal carotid)
- Hepatic vascular malformation
- Tachyarrhythmias
- Cardiomyopathy
- Other electrocardiogram abnormalities

SGBS-Limbs anomalies

- Broad hands
- Short hands
- Hypoplastic finger nails
- Postaxial hexadactyly
- Deep plantar creases
Speech characterized by a distorted articulation
Distorted resonance
Fluency failures
Stereotype prosody

SGBS- Other findings

- Anal atresia
- Hypospadias
- Pseudo hermaphroditism
- Severe mental retardation
- Hydrocephalus
- Epilepsy
- Obstructive sleep apnea

Young et al., Pediatr Neurol 2006;34:139-42; Paludetti et al., Int J Pediatr Otorhinolaryngol 2003;67:1143-7
SGBS- Evolving phenotype

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SGBS- Etiology & Causes

- X-linked gene: glypican 3 (GPC3)
- Maps Xq26
- GPC3: more than 500 kb and 8 exons.
- Protein: Glypican-3 has 580 amino acids.

Xuan et al., Hum Mol Genet. 1994 Jan;3(1):133-7
SGBS- Germinal Mosaicism

Germinal Mosaicism

Mother

Patients

No specific genotype-phenotype correlation

No major differences between patients with deletions and point mutations

Mariani et al., J Pediatr Endocrinol Metab. 2003 Feb;16(2):225-32
Beckwith Wiedemann syndrome

Macroecephaly-capillary malformation

Sotos syndrome

Non-syndromal OG with or without mental retardation
(Macrocephaly-Capillary Malformation)

- Overgrowth
- Capillary malformation
- Nevus flammeus
- Capillary malformation in the upper lip/philtrum
- Asymmetry/Hemihypertrophy
- Hemimegalencephaly
- Macrocephaly
- Polydactyly
- Mental retardation 50%
Differential Diagnosis - M-CM
Differ. Diagnosis- Beckwith Wiedemann
Differential Diagnosis - Sotos syndrome
Gpc3-deficient mice display a high incidence of:

- Ventricular septal defects, common atrioventricular canal and double outlet right ventricle.
- Delay in endochondral ossification
- Somatic overgrowth, renal dysplasia, accessory spleens, polydactyly, and placentomegaly
- Perinatal death, cystic and dyplastic kidneys, and abnormal lung development.
- Mandibular hypoplasia
- Imperforate vagina.

Chiao et al., 58: Dev Biol. 2002 Mar 1;243(1):185-206
Cano-Gauci et al., J Cell Biol 199;146:1; 255-264
Viviano et al., Dev Biol. 2005 Jun 1;282(1):152-62
SGBS-Transgenic mice

Mandibular hypoplasia
Complete lack of mandible in the mutant embryo.

Cano-Gauci et al., J Cell Biol 199:146:1; 255-264
Gpc3/DeltaH19 double mutants (bialellic expression of Igf2 gene by imprint relaxation),

- Omphalocele and skeletal defects.

- Compatible with a model positing that there is downstream convergence of the independent signalling pathways in which either IGFs or GPC3 participate

Chiao et al., 58: Dev Biol. 2002 Mar 1;243(1):185-206
Glypican-3 inhibits Hedgehog signalling during development by competing with patched for Hedgehog binding.

- GPC3 null embryos display increased Hedgehog signalling
- GPC3 inhibits Hedgehog activity
- GPC3 interacts with Hedgehog but not with its receptor, Patched
- GPC3 competes with Patched for Hedgehog binding.
- GPC3 induces Hedgehog endocytosis and degradation. The heparan sulfate chains of GPC3 are not required for its interaction with Hedgehog.
- GPC3 acts as a negative regulator of Hedgehog signaling during mammalian development and that the overgrowth observed in SGBS patients is, at least in part, the consequence of hyperactivation of the Hedgehog signaling pathway.

Capurro et al., Dev Cell. 2008;14:700-11
Direct interaction of GPC3 with CD26

GPC3 without the GPI anchor is capable of inducing apoptosis indicating that neither the GPI anchor nor the membrane attachment is required for apoptosis induction.

Davoodi J et al., Proteomics 2007;7:2300-10
Loss of glypican-3 induces alterations in Wnt signaling.

Matting of GPC3 knockout mice with insulin receptor substrate-1 (IRS-1) nullizygous mice.

- GPC3 regulates somatic growth independent of IRS-1,
- GPC3 does not modulate IGF signaling.
- GPC3 knockout mice exhibit alterations in the Wnt signaling pathway,
- GPC3 led to the inhibition of the non-canonical Wnt/JNK signaling pathway and activation of canonical Wnt/beta-catenin signaling.
- At least in some cell types GPC3 serves as a selective regulator of Wnt signaling, by potentiating non-canonical Wnt signaling, while inhibiting the canonical Wnt signaling pathway.
- SGBS may in part result from a loss of GPC3 controls on Wnt signaling and requires the cooperation of both the protein and the heparan sulfate moieties of the proteoglycan.

GPC3 bound specifically through its N-terminal proline-rich region to both Insulin-like growth factor (IGF)-II and IGF-1R.

GPC3 stimulated the phosphorylation of IGF-1R and the downstream signaling molecule extracellular signal-regulated kinase (ERK) in an IGF-II-dependent way.

GPC3 knockdown in HCC cells decreased the phosphorylation of both IGF-1R and ERK.

GPC3 confers oncogenecity through the interaction between IGF-II and its receptor, and the subsequent activation of the IGF-signaling pathway.

SGBS-Oncogenicity

- Wilms tumour
- Hepatoblastoma.
- Hepatocarcinoma
- Adrenal tumour

Surveillance for Wilms tumour

- Should be offered to children at >5% risk of Wilms tumour.
- Should only be offered after review by a clinical geneticist.
- Should be carried out by renal ultrasonography every 3-4 months.
- Should continue until 7 years.
- Can be undertaken at a local centre, but should be carried out by someone with experience in paediatric ultrasonography.
- Screen-detected lesions should be managed at a specialist centre.

Overgrowth Syndromes - Risk of Tumours

Beckwith-Wiedemann
n= 101

Sotos
n= 20

Simpson-Golabi-Behmel
n= 9

Perlman
n= 10

Hemihyperplasia
n= 133

Klippel-Trenaunay
n= 9

Proteus
n= 27

Gracia and Lapunzina, J Pediatr Endocrinol Metab. 2005 Dec;18 Suppl 1:1227
Simpson-Golabi-Behmel syndrome

- Rare, X-linked overgrowth syndrome
- Typical craniofacial features
- GPC3
- Mild to moderate mental retardation
- Tumour risk
- Surveillance for embryonal tumours